REMARKS

Favorable reconsideration, reexamination, and allowance of the present patent application are respectfully requested in view of the foregoing amendments and the following remarks.

I. CLAIM STATUS & AMENDMENTS

As correctly stated in the Office Action Summary, claims 1-4 were pending in this application when last examined. Claims 1-4 have been examined on the merits, and stand rejected. The present amendment amends claims 1-3 and adds new claims 5-10. The present amendment also cancels claim 4 without prejudice or disclaimer thereto. Claims 1-3 and 5-10 are pending in this application.

Applicants reserve the right to file a continuation or division application on any canceled subject matter.

Support for the amendments to claim 1 can be found in the Specification, for example, at page 4, lines 1-5, 19-20, page 5, lines 1-2, and original claim 1. Support for the amendments to claim 3 can be found in the Specification, for example, at page 4, lines 16-22, page 5, lines 18-25, and original claim 3. Support for new claims 5 and 6 can be found in the Specification, for example, at page 6, lines 1-4, page 10, lines 13-14, pages 8-11, Example 1 (Table 1), and in original claim 1. Support for new claims 7 and 8 can found in the Specification, for example at pages 11 and 12, Example 2 (Table 2), and in original claim 1. Support for new claims 9 and 10 can be found in the Specification, for example, at page 6, lines 4-10, and pages 12-14, Example 3 (Tables 2-3), and in original claim 1.

The Specification has also been amended to correct inadvertent typographical errors. Support for such amendments can be found in the Specification as originally filed.

Therefore, no new matter has been added by this amendment.

II. FORMAL MATTERS

A. Applicants' Priority Date

Acknowledgment has been made of the claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f), as well as receipt of all certified copies of the foreign priority documents. See September 26, 2003 Office Action page 1, Item 13.

B. Objection to the Specification

The Specification has been objected to as allegedly containing grammatical, idiomatic, and spelling errors, *e.g.*, the term "antigenicity" on page 5, line 12, and page 7, lines 12 and 21 is misspelled . See September 26, 2003 Office Action, page 2.

The present amendment amends the Specification to correct these inadvertent typographical errors, thus obviating this objection. Accordingly, Applicants respectfully request the withdrawal of this objection.

III. REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

Claims 1-4 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. See September 26, 2003 Office Action, pages 2-3. Applicants respectfully traverse this rejection as applied to the amended and new claims.

The Examiner contends that it is allegedly unclear how the measuring steps relate to the immunoassay preamble of claims 1-4. The Examiner further contends that it is allegedly unclear regarding what reagents the thrombin and/or antibodies are added to. These claims have been amended to recite that the thrombin and/or antibodies are added to a serum or plasma test sample. Thus, it is clear that the thrombin and/or antibodies are added to a serum or plasma test sample.

Moreover, the Specification teaches that these compounds are added to the serum or plasma test sample utilized in an immunoassay method, such as a two-step sandwich assay. Specification, page 6, lines 1-10. It is well settled that the test for definiteness is whether those skilled in the art would understand what is claimed when the claim is read in light of the

specification. See Orthokinetics, Inc. v. Safety Travel Chairs, Inc., 806 F.2d 1565, 1576, 1 U.S.P.Q.2d 1081, 1088 (Fed. Cir. 1986); M.P.E.P. § 2173.02. Based on the disclosure in the Specification, those skilled in the art would clearly understand that the thrombin and/or antibodies are added to a serum or plasma test sample in an immunoassay. Thus, contrary to the Examiner's position, the interrelationship between the steps and the preamble of the claim is clear and definite.

Regarding the recitation "fibrin-like related substances," the Examiner contends that there is no standard for ascertaining the requisite degree of relatedness. Amended claims 1-3 recite "fibrin related substances." The Specification clearly indicates that fibrin related substances include fibrinogen, fibrin, FDP, fibrinopeptide A, and fibrinopeptide B. Specification, page 4, lines 19-22, and page 5, lines 19-21. Given such a disclosure, those skilled in the art would clearly understand what is meant by "fibrin related substances." Thus, the recitation "fibrin related substances" is clear and definite.

Amended claim 1 recites that the thrombin is added to the serum or plasma test sample. This amendment obviates the Examiner's concern regarding how the "thrombin" of dependent claim 2 is used. Similarly, amended claim 1 also recites that the antibodies are added to the serum or plasma test sample. This amendment obviates the Examiner's concern regarding how the antibodies are used.

Claim 4 has been canceled, thus obviating the Examiner's position that claims 3 and 4 cover identical subject matter.

Therefore, in view of the foregoing amendments and/or remarks, Applicants respectfully request the withdrawal of these rejections.

IV. REJECTIONS UNDER 35 U.S.C. § 103

Claims 1-4 stand rejected under 35 U.S.C. § 103(a), as allegedly unpatentable over Matsuda et al., U.S. Pat. No. 4,780,410 ("Matsuda"), in view of Lämmle et al., CLINICS IN HAEMATOLOGY, Ch. 1: Formation of Fibrin Clot: the Balance of Procoagulant and Inhibitory

Factors, Vol. 14, No. 2, pp. 281-285 (Ruggeri, ed., W.B. Saunders Company, London, 1985) ("Lämmle"), and Weir, HANDBOOK OF EXPERIMENTAL IMMUNOLOGY, Mouse immunoglobulin allotypes, p. 12.13 (Blackwell Scientific Publications, Oxford, 1978). See September 26, 2003 Office Action, pages 3-5. Applicants respectfully traverse this rejection as applied to the amended and new claims for the following reasons.

The cited art references fail to render the claimed invention obvious because they fail to teach and/or suggest each and every element of the claimed invention, namely, the step of adding thrombin and/or antibodies which specifically bind to a human fibrin related substance to a serum or plasma test sample in an immunoassay method.

To establish obviousness, three criteria must be met. First, the prior art references must teach or suggest each and every element of the claimed invention. See In re Royka, 490 F.2d 981, 180 U.S.P.Q. 580 (C.C.P.A. 1974); In re Zurko, 111 F.3d 887, 888-89, 42 U.S.P.Q.2d 1476, 1478 (Fed. Cir. 1997); In re Wilson, 424 F.2d 1382, 1385, 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970); M.P.E.P. § 2143.03. Second, there must be some suggestion or motivation in the references to either modify or combine the reference teachings to arrive at the claimed invention. See In re Vaeck, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991); M.P.E.P. § 2143. Third, the prior art must provide a reasonable expectation of success. See Vaeck, 947 F.2d at 488, 20 U.S.P.Q.2d at 1438; In re Merck & Co., Inc., 800 F.2d 1091, 231 U.S.P.Q. 375 (Fed. Cir. 1986); M.P.E.P. § 2143.02.

In this case, the primary reference of Matsuda fails to teach and/or suggest the addition of thrombin and/or antibodies that specifically bind to a human fibrin related substance to a serum or plasma test sample in immunoassay. Matsuda never discloses the use of thrombin in an immunoassay. Nor does Matsuda disclose antibodies that specifically bind to a human fibrin related substance, and their use in an immunoassay. Instead, Matsuda teaches a general enzyme sandwich immunoassay for determination of PIVKA-II utilizing an immobilized anti-PIVKA-II monoclonal antibody. Thus, Matsuda fails to teach and/or suggest the claimed invention.

The secondary references of Lämmle and Weir also fail to teach and/or suggest the addition of thrombin and/or antibodies that specifically bind to a human fibrin related substance to a serum or plasma test sample in immunoassay. Lämmle discusses the structure of PIVKA-II, and prothrombin, which is a thrombin precursor. However, Lämmle does not teach the use of prothrombin or thrombin in an immunoassay. Nor does Lämmle teach the use of antibodies specific to a fibrin related substance in an immunoassay. Lämmle never discusses an immunoassay for PIVKA-II, let alone one where thrombin and/or antibodies that specifically bind to a human fibrin related substance are added to the test sample.

Weir also never discusses the use of thrombin and/or antibodies to fibrin related substances, nor immunoassay methods utilizing such compounds.

Moreover, there is no suggestion and/or motivation in any of the cited references to add thrombin and/or antibodies that specifically bind to a human fibrin related substance to a serum or plasma test sample in immunoassay for PIVKA-II. As discussed in the background section of the Specification, prior to Applicants' invention, PIVKA-II had been measured by immunoassays resulting in poor sensitivity with a low positive rate. Applicants discovered that this poor sensitivity was due to unknown reaction substances in the test sample which interfered with the conventional assays. These unknown reaction substances resulted in positive errors in the measurement of PIVKA-II. Applicants further found that this interference was due to the presence of fibrin related substances in the samples. The instant invention solved this problem in the prior art. Applicants were the first to discover that the sensitivity and specificity for PIVKA-II could be improved by adding thrombin and/or antibodies that specifically bind to a human fibrin related substance to a serum or plasma test sample in an immunoassay.

The cited prior art never discusses the above-discussed problems associated with the conventional immunoassays for PIVKA-II. The cited prior art never suggests a solution for overcoming the problem associated with the prior art. Instead, the Examiner contends that the addition of soluble antigen, such as thrombin would have been expected to improve the specificity of a multispecific antiserum for the detection of PIVKA-II in serum as taught by Weir in view of

the known structures of prothrombin and thrombin as taught by Lämmle. The Examiner further contends that the variable levels of thrombin present in a sample of serum would unpredictably affect the proportion of antibodies in the polyclonal reagent available for binding to the target antigen.

Applicants respectfully submit that the Examiner's position regarding Weir is in error. Weir never suggests that the specificity of an immunoassay will be improved by the addition of soluble antigen, such as thrombin, to a reaction sample in an immunoassay. Weir never suggests that is it common to add soluble antigen, such as thrombin, to a reaction sample in an immunoassay. Weir never discusses the interference discussed above regarding enzyme immunoassays for PIVKA-II and whether it is attributable to bound or free thrombin in a sample. Weir never discusses the use of thrombin in an immunoassay. Instead, Weir discloses a method whereby antisera is absorbed with antigens rendered insoluble by covalent binding to an insoluble support such as Sepharose. See Weir, page 12.13, 1st column, last paragraph to 2nd column, first paragraph. Such a disclosure fails to teach and/or suggest adding thrombin and/or antibodies specific to fibrin related substances to an immunoassay to improve the specificity for PIVKA-II. There simply is no suggestion in the cited prior art to combine the references to arrive at the claimed invention with a reasonable degree of success.

Furthermore, Applicants submit that the vastly improved specificity for PIVKA-II demonstrated for the claimed invention as compared to that of conventional immunoassays, as evidenced in Tables 1-3 on pages 11, 12, and 14 respectively, amounts to a showing of surprising and unexpected results. It is well settled that a showing of surprising and unexpected results is sufficient to overcome a prima facie case of obviousness. See In re Albrecht, 514 F.2d 1389, 1396, 185 U.S.P.Q. 585, 590 (C.C.P.A. 1975); M.P.E.P. § 2144.08.

Thus, in view of the above, the claimed invention is not obvious over the cited references because the cited references fail to teach each and every element of the claimed invention, and they lack a suggestion to combine/modify the reference teachings to arrive at the claimed invention. Therefore, Applicants respectfully request the withdrawal of this rejection.

CONCLUSION

For at least the foregoing reasons, Applicants respectfully submit that the present patent application is in condition for allowance. An early indication of the allowability of the present patent application is therefore respectfully solicited.

If Examiner Grun believes that a telephone conference with the undersigned would expedite passage of the present patent application to issue, he is invited to telephone the undersigned at the number below.

Respectfully submitted,

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